What is meta-analysis? What assumptions does it make? And what common biases may be present?

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Title: What is meta-analysis? What are the assumptions and common biases?

Running title: Interpretation and understanding of meta-analysis

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Introduction

Treatment efficacy is best assessed with randomised controlled trials (RCTs). Often multiple RCTs compare the same interventions and intervention decisions should consider this evidence. Meta-analysis gives a weighted average of treatment effects from multiple studies making similar comparisons. To pool studies using meta-analysis requires the same effect measure, (e.g. Relative risk, mean difference) together with its standard error, or sufficient information to calculate them (e.g. numbers of patients and events in each arm for binary outcomes), from each study.

Assumptions and Heterogeneity

Meta-analysis requires assumptions. Most meta-analyses use fixed or random effect models. Fixed effect models assume the treatment effect is identical across trials and each trial's weight is directly proportional to the precision of its estimate. But trials differ. They recruit different patients, sometimes from different settings, with different demographics, and different risks of outcome. Interventions may differ in dose, route, etc. Trial methodology may differ in method of randomisation, statistical analysis etc.

These variations between studies may lead to differences in the (unknown) underlying treatment effects. This is heterogeneity. When heterogeneity is present a random effect model should be used. It assumes the different underlying treatment effects vary randomly around a population average and accounts for this in the weighted average. Heterogeneity is usually quantified using the I-squared statistic: the estimated proportion of the variation in results attributable to heterogeneity. Prediction intervals show the distribution of likely underlying treatment effects for a new study. When heterogeneity is high results may not be meaningful and meta-analysis not appropriate. But, pre-planned subgroup analyses sometimes partially explain heterogeneity.

Bias

Even when statistical assumptions are reasonable, biases can result from study quality, or study selection. Studies should be identified through a systematic review. But studies may be unavailable or unidentifiable and included studies may not be representative. Publication bias occurs if studies with positive findings are more likely to be published or are published quicker than those without. Reporting bias occurs if published studies collecting data for multiple outcomes only report outcomes with positive results. If enough published studies are identified, statistical methods can sometimes identify bias.

Example

Daley[1] assessed exercise for prevention and treatment of antenatal depression. They identified six relevant trials through systematic review. The data were heterogeneous so they use a random effect model estimating an improvement in standardised mean difference in depression scores of: 0.46 (95%CI -0.87,-0.05) (figure 1). Planned subgroup analysis did not reduce heterogeneity. They

conclude that there is some evidence of effectiveness but 'the conclusion is based on a small number of low-moderate quality trials with significant heterogeneity and wide confidence intervals'.

Etiological, diagnostic, prognostic, prevalence and incidence studies can also be meta-analysed.

RESOURCES

The Cochrane Collaboration[2] provide guidance for systematic reviews and meta-analysis

LEARNING POINTS

Treatment decisions should utilise all relevant evidence which is often synthesised using meta-analysis.

Differences in study populations and design may cause heterogeneity. This may be modelled and/or assessed through subgroup analysis.

Even when statistical assumptions are reasonable, bias can result from study quality, identification, or reporting.

Figure Captions

Figure 1. Forest plot, summary results and assessment of heterogeneity for Primary meta-analysis of all trials for antenatal depression scores Re-produced from Daley et al[1]. The comparison Field (2012) (c1) refers to yoga versus usual care. The comparison Field (2012) (c2) refers to yoga versus massage.

REFERENCES

1. Daley AJ, et al. BJOG 2014;122(1):6.

2. Higgins JPT, et al(editors). The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.

Disclosure of Interests

None